# THE SEQUELÆ OF EPIDEMIC ENCEPHALITIS.[1]

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At the height of an epidemic the attention of the medical world is focussed on immediate results rather than on after-effects. "Will the patient recover or die?" is the prognostic question above all others. When, however, the fire of the epidemic has burnt itself out and we begin to take stock of the condition of the survivors, other questions press for an answer. "Are certain disabilities to be regarded as temporary or permanent?" "When the patient has made an apparently complete recovery, is all well with him or is anything more to be feared?"

The answer to such questions can already be given in the case of influenza. Many a patient recovers from the disease only to be left a weakling for the rest of his life, open to the attacks of the tubercle bacillus and other invaders of the respiratory tract. What can be said of the recent outbreak of epidemic encephalitis?

In estimating the permanence of the damage done by the virus of epidemic encephalitis it is often difficult to separate what may with justice be called an after-effect from merely a long-continued manifestation of the disease. Sometimes symptoms may persist so long that we may with reason class them as sequelæ. Other after-effects succeed the illness only after an interval of varying duration.

The first cases of the disease appeared in Winnipeg in October, 1919. An analysis of 75 cases personally investigated together with the autopsy findings in 16 cases has been published in previous papers.[1] The worst of the epidemic was over by the end of January, 1920. Sufficient time, therefore, has elapsed to enable some estimate to be made as to the degree of completeness of recovery and to determine whether any untoward after-effects may be expected.

It may be said at once that in our experience complete and rapid recovery is uncommon except in really mild cases, that many patients continue to suffer from some of the symptoms in modified form, and that in a few there appear new symptoms which must be regarded as true after-effects. Of 31 patients who have been communicated with, 20 complained of symptoms after all the acute manifestations of the disease had disappeared.

For convenience of description the symptoms may be divided into four main groups: (1) General; (2) paretic (cranial nerves); (3) irritation; (4) parkinsonian.

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[1] Boyd, W.: The Winnipeg Epidemic of Encephalitis Lethargica, Can. Med. Assn. Jour., February, 1920. Epidemic Encephalitis: A Study of Seventy-five Cases with Sixteen Autopsies, Ann. Med., July, 1920.

1. *General Symptoms.* In those recovering from encephalitis perhaps the most common complaint is marked general asthenia, which may last for many months. There is the same lack of energy and initiative so characteristic of the convalescence from influenza, but it is even more marked in degree. A large proportion of the patients reached by our "follow-up" system complained of this asthenia. In some cases it was many months before the patient began to recover strength. One patient was still very weak six months after the onset of the illness.

The explanation of the asthenia is open to doubt. If lethargic encephalitis is regarded as purely an affection of the central nervous system the asthenia may be due to exhaustion of the nerve cells. If, on the other hand, it is a true, systemic infection, with special localization in the central nervous system, as in the writer's opinion is the case, the asthenia may be similar in nature to that following such general infections as influenza and typhoid fever.

Headache, or a sense of fulness or discomfort in the head, has been a common after-effect. It is most frequently occipital in type, but it may involve any region.

Alteration in the temperament has been observed in a number of our cases, sometimes with definite evidence of mental disturbance. One girl, aged six years, after a typical attack of lethargic encephalitis, made a good recovery. Three months later her parents reported that her disposition had undergone a complete change. From being a bright, playful child she had become dull and apathetic and would sit for hours motionless in a chair, almost like one suffering from myxedema. A peculiar feature was an occasional loss of bladder control, more especially at night.

At least three of the cases have developed mental symptoms. In two of these delusions were the most prominent feature. In the third there was a general mental deterioration, accompanied by loss of memory and inability to focus the attention.

One patient, after spending three weeks in the hospital, during which he presented a typical picture of the disease, was discharged as improved. Two weeks later he developed an erythematous rash on the neck, arms and body, which was intensely itchy and lasted for about a week. His subsequent recovery was unusually delayed, and even now, nine months later, he has by no means completely recovered his strength.

Occasionally the apathy and torpor characteristic of the acute stage of the disease establish themselves as apparently permanent features of the patient's mental constitution and the flash and speed of the mind are lost forever. One such case reminds one irresistibly of the description given by the Arab physician Karshish in Browning's poem:

> "He listened not except I spoke to him,
> But folded his two hands and let them talk,
> Watching the flies that buzzed."

Whether the mental processes of such a patient will ever return to normal it is at present impossible to say. It appears not unlikely that he will gradually sink into a state of dementia.

An interesting example of what may be considered as the general after-effects of encephalitis is the following:

Mr. W. K., aged sixty-six years, suffered from a characteristic attack of epidemic encephalitis in November and December, 1919. The outlook for some time was extremely grave, but eventually he made a wonderfully good recovery and was discharged from the hospital just before Christmas. An account of the case, with a photograph of the patient, has already been published. For some time he remained perfectly well and was able to take part in the work of a farm. About a month later, however, he began to experience a weakness which gradually increased until he was no longer able to work. He would wake up in the morning feeling fresh and fit for work, but in the course of half an hour he would be quite exhausted and fit for nothing but to lie down. From being quite alert mentally he again lapsed into an apathetic and sleepy condition, dropping off to sleep at a moment's notice. About the same time he began to suffer from stiffness and "rheumatic pains" in many of his joints. The stiffness of the arms was so pronounced that he was unable to put on his coat. His hands became swollen and puffy and later desquamated. At the time of the original illness diplopia was a prominent symptom. It disappeared with recovery, but with the onset of these fresh symptoms it reappeared, although only at occasional intervals. A humming noise in the ears was also noticed.

When seen by me for the second time, on August 10, 1920, I was at once struck by his dull, heavy, bucolic look, which was much more marked than at the time of discharge. It was not the mask-like face of Parkinson's disease, seen so frequently in these cases. Rather did it remind one of the appearance in myxedema; there was the same yellow tint, the same broad, heavy look, the same puffiness of the face—a condition, indeed, to which the patient himself made reference. Slight weakness and tremors of the left side of the face recalled the facial paralysis on that side from which he had suffered during the initial illness. All the reflexes were normal. There was some desquamation on the chest and on the back of both hands. He was able to converse perfectly rationally, but cerebration was very slow and the memory was defective. He complained of copious salivation and severe constipation.

The general impression produced on the observer was that of a person in whom both the physical and mental peculiarities were due to hypofunctioning of the thyroid. I know of no case recorded in which definite thyroid disease could be attributed to epidemic encephalitis. That such may occur, however, was shown by one case in my own experience. A young woman had previously suffered from exophthalmic goiter, but for four years she had shown no signs of hyperthyroidism, although presenting a slight degree of exophthalmos. Following an attack of encephalitis, however, the symptoms of hyperthyroidism returned in full force, and she now presents a typical picture of Graves's disease. I greatly regret that in a series of eighteen autopsies on cases of epidemic encephalitis I omitted to examine the condition of the thyroid in every instance.

The case of Mr. K., just recorded, affords a good example of true sequelæ, the consequences of the disease. Occasionally, however, one meets with what appears to be a relapse or recrudescence of the original trouble. Economo[2] reports a remarkably interesting case of this description in which there were several severe attacks, separated by periods of remission. He died two years after the onset of the illness. The brain showed numerous lesions, both recent and old, characteristic of epidemic encephalitis.

One case of this description has occurred in our experience.

Mr. D., aged twenty-seven years, was admitted to the hospital on June 15, 1920. Three days before he was overcome by weakness while at work and the next day was confined to bed. On admission he was in a drowsy, stuporous condition, although restless and excited at night. He was unable to answer questions and did not appear to be conscious of his surroundings. The temperature fluctuated between 101° and 103° for eighteen days, when it returned to normal. About the same time there was marked improvement in both his physical and mental condition. By July 24 he was sitting up in bed and on August 6 he was out on the sun-balcony, bright and cheerful, and apparently well on the road to recovery. About August 16, however, he again began to show signs of physical lethargy and mental torpor. Fever returned, the temperature varying between 100° and 101°. Speech became increasingly difficult and finally he was unable to open his mouth.

When I saw him on August 20 he was lying like a log in bed, flat on his back, with his hands folded across his chest like an effigy on a tomb. Apart from following one about the room with his eyes he showed no sign of life. He was unable to open his mouth or to make any movements except to raise or lower the hand a little way, by means of which he was able to signify yes or no to a question. Cerebration, as judged by such response, was markedly delayed. There was slight facial weakness on the right and distinct ptosis on the left side. The right pupil was larger than the left. Both fundi showed a low grade of neuroretinitis. This process, in the opinion of the ophthalmologist, was early. The most painful stimuli produced no change in the facial expression, but when asked if he felt pain he signified in the affirmative. Both knee-jerks were increased and on the left there was persistent ankle-clonus and a positive Babinski sign. The urine was normal and the cerebrospinal fluid showed a slight increase of globulin. A couple of days later the temperature fell to normal, the ptosis disappeared and he was able to make monosyllabic replies. Apart from this, however, there has been no improvement.

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[2] Economo: Subacute lethargic encephalitis, Wien. Arch. f. inn. Med., June, 1920.

The interest of this case lies in the fact that it is apparently an example of a true relapse. The return of fever, the ptosis, the Babinski sign and the lethargy all suggest a recrudescence of the disease rather than an epiphenomenon developing as a consequence of vascular or other derangement.

A few brief summaries from the "follow-up" records may be given as illustrating the subsequent history of some not unusual cases:

Mr. N. suffered from a severe attack of epidemic encephalitis in December, 1919. It was remarkable for extremely violent myoclonic spasms of the rectus and other abdominal muscles, which continued over a period of several weeks. He made a good recovery. In June, 1920, he says that he feels well except for tiredness, which is worse in the morning and passes off toward the evening. Works in a store about three hours a day and spends the rest of the day lying down. Tremors have all gone. His weight, which before his illness was 145 pounds, is 158 pounds.

Mr. R. Recovered from a severe attack at the beginning of January, 1920. In May he says that he feels "Not too bad and not too good." Complains of "soreness" on the top of the head, in the stomach region and in left thigh. He is now back at work.

Miss L. was discharged from the hospital as "improved" at the end of February, 1920. In June she was still listless and apathetic, with vacant expression and unable to read for more than a few minutes at a time.

Miss K. was discharged from the hospital on December 18, 1919. At first she had presented a picture of acute paralysis agitans, followed later by lethargy and somnolence. In September, 1920, she says that she has never felt well since leaving the hospital. Complains of general weakness, headache, "rheumatic pains" in hip and shoulder and stiffness in ankles and feet. Occasional attacks of well-marked diplopia.

2. *Paretic (Cranial Nerves).* Evidence of prolonged cranial nerve involvement has been observed in a number of cases. In several instances in which facial paralysis was a feature of the disease proper a lingering weakness has been detected many months later. In none of our cases, however, has the paralysis been complete or even pronounced.

Diplopia has been a more common symptom. In some cases it was a feature from the beginning of the illness; in others it came on after an interval of apparent recovery. The mechanism of such recurrence will be discussed later in this paper.

Weakness of accommodation is perhaps the most frequent indication of cranial nerve weakness. For many months patients have been unable to read except with the aid of glasses, and there may be permanent impairment of vision. A marked example of this condition is the following:

A. M., a returned soldier, suffered from a typical attack of epidemic encephalitis in the beginning of December, 1919. When he began to recover from the illness toward the end of the month he found that he was unable to read. With the aid of +3D glasses he could read with perfect ease. A subsequent examination made in August, 1920, showed that no improvement had taken place in the eye condition and that paralysis of accommodation was still complete.

Of the cranial nerves involved the most important is the optic. During the acute stage of the illness optic neuritis is very uncommon. There has not been a single instance in our series, although careful ophthalmoscopic examinations were made in nearly all the cases. In several cases congestion of the vessels and slight haziness of the edges of the disk were noticed. Notwithstanding this absence of evidence of acute inflammation there were at least two cases of undoubted optic atrophy. In one of these there was marked dimness of vision two months after recovery from the acute attack and the patient was unable to distinguish colors at two feet. A marked secondary optic atrophy was found on ophthalmoscopic examination. The second case, seen six months after the onset of the illness, was also marked by great dimness of vision, and the ophthalmologist's report was as follows: "On the right side the pupil is widely dilated, with complete loss of reaction to light. There is a marked degree of optic atrophy. The retina around the disk shows considerable degeneration. Evidently a low-grade inflammatory condition. In the left eye the pupil reacts very slightly to light. There is commencing optic atrophy. The retina around the disk shows the same condition of progressive low-grade chronic inflammation as is seen on the right side. One patch about 1 mm. in diameter just below the disk shows complete degeneration, but the retina all around the disk is partially degenerated and grayish in appearance."

3. *Irritation Group.* The most remarkable of the sequelæ of epidemic encephalitis in the experience both of such observers as of Farquhar Buzzard[3] and of ourselves have been motor disorders of the nature of spasms, automatic, athetoid and choreiform movements. These may merely form a continuation of the clonic movements so frequently observed in encephalitis, and especially affecting the abdominal muscles, or they may arise *de novo* in a patient never previously exhibiting such phenomena.

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[3] Encephalitis Lethargica, Proc. Roy. Soc. Med., 1919, No. 9, vol. xii.

The following case is an example remarkable for its extremely long duration and for the fact that there were no intervals or intermissions.

Mr. N., aged twenty-five years, was admitted to the hospital at the beginning of January in a dull and apathetic condition. The temperature was 102°. He lay in bed, staring at the ceiling in a stupid, cow-like fashion. The cerebrospinal fluid was under high pressure, 80 c.c. being withdrawn. The cells and globulin were normal. He soon lost the power of speech, there being actual difficulty in articulation. Although extremely emaciated he exhibited a ravenous appetite and suffered from intense thirst. Despite a marked degree of polyuria, sugar was never present on any occasion. Toward the middle of March tremors began to appear. These were well marked on both sides of the face and about the mouth, and also in the hands and arms, but the left leg only showed slight tremors. The abdominal muscles were not affected. The corners of the mouth were retracted about seventy-five times per minute. The twitchings of the hands were rhythmic, being faster on the left side than on the right. On one day those on the left were 240 and on another 188 per minute. The thumb and fingers of the left hand showed typical cigarette-rolling movements. There were periods of complete rest. The face was frequently bathed in profuse perspiration. The twitchings continued unabated until the patient's death which occurred early in July, six months after the onset of the disease. I did not have an opportunity to examine the brain.

In such a case it is difficult to speak of sequelæ, for the patient never appeared to emerge from the mental stupor characteristic of the onset of his illness. At the same time an interval of ten weeks clapsed before the development of the tremors.

There have been no cases in our series which have developed involuntary movements after an interval of perfect health, as in the many striking cases described by Buzzard. The following case, however, for a description of which I am indebted to Dr. Gordon Bell, affords an interesting example of an automatic action from an imperative idea developing during convalescence.

Mr. M., aged forty-five years, walked into the laboratory, sat down and crossed his right leg over his left. There were a number of people in the room at the time and he was not attended to at once. After sitting perfectly still for a minute he suddenly arose and walked around the room, from left to right, with a gait so peculiar that it is difficult to describe. It had the stiff, automaton-like character of the sentry-go, but in an almost grotesque degree. Having completed the circle he sat down and crossed the right leg over the left, all the time with a face expressionless and inscrutable as the sphinx, save for a peculiar twitching of both upper eyelids. A minute later he repeated the performance, nor did it differ from the preceding one by a hair's breadth. When taken into an adjoining room and examined he was afraid of being laughed at and explained that he was utterly unable to help himself. He gave a typical history of epidemic encephalitis. Nearly a month ago he was seized one day with weakness in the legs, and on getting up the next morning found that he was unable to shave, as he saw two faces and two razors. The diplopia lasted for a few days and was then replaced by the double facial paralysis, which was still so much in evidence. The entire face was immobile, except for marked tremors and twitchings of the upper lids. A peculiar and interesting symptom was marked parosmia: he was constantly aware of disagreeable smells, and this proved to be the most lasting of his symptoms. At this stage in his recital he jumped to his feet and went through his customary evolution. He then explained that this distressing complication had developed during the period of convalescence, that he was wholly unable to control the impulse and that it was not to relieve any peculiar sensation in the legs, but because of something he felt inside his head, that he was compelled to behave in a manner he felt to be so ridiculous. He put his feet up on the table and vowed that he would stick to his chair, but the flesh proved too weak. The subsequent history was that the patient gradually improved, and in the course of a few months he was free both of his facial paralysis and his distressing automatism. The parosmia, however, still persists.

In a recent paper by Buzzard several examples are given of involuntary movements coming on many months after the initial illness. This illness occurred in one case in May, 1918. In September of the same year the patient noticed involuntary twitching of the right toe, which spread until it affected the greater part of the right leg and right shoulder. In December the right arm displayed spasmodic contractions every one or two seconds, which caused it to be thrown behind the trunk or slightly elevated. Clonic contractions occurred in the muscles of both buttocks and in the right thigh and leg. There were irregular rotatory movements of the abdominal wall and umbilicus. In another case constant movements of both shoulders appeared six months after an attack of epidemic encephalitis; the movements are described as being "trouser hitching" in character. Contractions of several groups of muscles in the legs were observed, and there were also forced movements of the head.

4. *Parkinsonian Group.* Many groups and subdivisions of epidemic encephalitis have been suggested. A long list of these is given in Tilney and Howe's recent monograph.[4] They may all be collected into three great classes, depending upon the brain level mainly involved. These are the upper cerebral or cortical group,

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[4] Tilney and Howe: Epidemic Encephalitis, New York, 1920.

comprising a comparatively small number of cases manifesting such symptoms as hemiplegia, hemianopia, spasms and convulsions; the thalamic group with symptoms suggestive of Parkinson's disease; and the brain-stem group in which involvement of such cranial nerves as the oculomotor and facial is often associated with varying degress of somnolence. It is true that the disease process refuses to be confined to water-tight compartments, but for descriptive purposes such a classification is convenient.

In any considerable group of cases of encephalitis many examples of what may be called the Parkinsonian type will be encountered. Our series has provided some striking pictures of paralysis agitans, although without the characteristic tremor. A case described by Russel[5] bore a close resemblance to progressive lenticular degeneration, including the peculiar emotional disturbances. We have observed that such cases are slower in clearing up than are those of any other group. Not only are the symptoms persistent, but it almost appears as if in these cases the lesion were progressive.

A case in point is the following:

Mr. Z., aged twenty-three years, was under observation for nearly a month in the Winnipeg General Hospital suffering from epidemic encephalitis. At the commencement of his illness the chief features were restlessness and insomnia, but these were soon replaced by marked lethargy and drowsiness. The face acquired the mask-like appearance of Parkinson's disease, and when he was able to be up the posture and gait were also suggestive of that condition. He made a fairly good recovery, but even on discharge his face lacked that play of emotional light and shade which distinguishes the normal individual. When seen eight months later he was markedly worse. Some progressive lesion had apparently been at work. He sat leaning forward in his chair with the blank, expressionless face of a mask. He walked with a shuffling gait, the back bent forward, the arms flexed at the elbow and the hands at the wrist, the rigid gaze fixed on the ground. He had been unable to work for some months and there was a considerable degree of mental impairment. The pupils did not react to light, and the optic atrophy and retinal degeneration already described in an earlier section were observed on ophthalmoscopic examination. The picture presented was one of Parkinson's disease without the tremor.

In the next case the patient never completely recovered his health. At the same time the Parkinsonian features did not develop for some months, so that they may with justice be regarded as true sequelæ. For the details of this case I am indebted to Dr. A. T. Mathers.

Mr. M., aged sixty-two years of age, at the beginning of January, 1920, began to see double and suffered from insomnia, but later became very lethargic and drowsy. He was in bed for three weeks and has not been well since. At the present time (September, 1920) he complains of constant headache, of a feeling of dizziness or light-headedness, of clumsiness of the right side of the body and of an increased secretion of saliva. The face is immobile and expressionless. The gait is clumsy and he sways slightly as he walks. The right arm hangs as if useless and can only be used clumsily, but is not deficient in power. The right leg shares in the clumsiness. There is slight rigidity of the muscles on the right side of the body and the deep reflexes on that side are distinctly exaggerated. Adiadokokinesia and asynergia are marked on the right side. Vision is failing rapidly and ophthalmoscopic examination shows indistinctness of the margins of both disks, which are redder than they should be and are covered with numerous small vessels. The cerebrospinal fluid shows a slight increase in globulin, but is otherwise normal.

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[5] A Study on Epidemic Encephalitis, Based on the Study of Seventeen Cases with Two Autopsies, Canada Med. Assn. Jour., August, 1920.

Tilney and Howe describe a case very similar to the above: Ten months previously their patient had suffered from an acute illness associated with dulness, stupidity and somnolence. A few weeks later paralysis of accommodation developed, together with weakness of the right side of the face and tongue, and the right arm and leg. On examination marked clumsiness and stiffness of the right arm and hand were observed, and to a lesser degree of the right leg. There was paresis of the right side of the face and tongue. The condition is described as hemilateral paralysis agitans without tremor.

In our own case two elements may be distinguished, the thalamic and the cerebellar. A lesion in the hypothalamus involving nerve paths running from the red nucleus through the superior cerebellar peduncle to the dentate nucleus of the cerebellum might account for all the symptoms.

The mechanism by which the sequelæ are produced may now be considered briefly: In order to form a conception of what may occur it is essential to have a clear picture of the condition of the brain when the acute attack is over. The brain substance has been the seat of an inflammatory process, the brunt of which has fallen not on the nerve cells but on the interstitial tissue. An inflammatory exudate has been formed, mainly perivascular in type, but also extending into the surrounding brain substance, and in the more severe cases hemorrhage and thrombosis are present, accompanied by a corresponding degree of tissue disintegration and degeneration. Such a condition in any other part of the body would be followed by organization and repair, with fibrosis, and in the brain fibrosis when once started is by no means a self-limited process.

The net result of all this is interference with nerve paths. Positive symptoms, as Hughlings Jackson long ago pointed out, cannot be produced merely by negative or destructive lesions, and must be attributed to the uncontrolled action of nervous impulses normally held in check. It is probable that many of the involuntary and spasmodic movements may be traced to the overaction of primitive motor paths arising in the thalamic region, just as similar movements in progressive lenticular degeneration are due to lesions in the lenticular nucleus.

To one familiar with the microscopic picture in any large series of cases of epidemic encephalitis the wonder is not that after-effects are common, but that, to any marked degree at least, they are comparatively rare. We cannot leave the uncertain ground of hypothesis until more observations have been made on the condition of the brain in encephalitis after a considerable interval has elapsed. Greenfield[6] has described extensive calcification of the vessels in a case which died four months after the acute illness. Should such an occurrence be shown to be frequent, it is an observation of great importance.

Little is to be gained, however, by idle speculation until a greater mass of pathologic evidence is available, and the future will no doubt shed fresh light both on the clinical manifestations of the disease and on the pathological changes which form their substratum.

I am greatly indebted to Dr. F. C. Bell, director of records in the Winnipeg General Hospital, for assistance in tracing the after-history of many of the patients in that institution.

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# MECHANISM OF LOWERED RESISTANCE FOLLOWING EXPOSURE TO LOWERED TEMPERATURE.

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The following study was undertaken for the purpose of ascertaining if possible the functional and structural changes which follow chilling of the body surface and which lead directly or indirectly to disease. The belief has long been held by clinicians and investigators that when the surface of the body is chilled, certain of the internal organs, particularly the respiratory organs, become more susceptible to bacterial invasion. Other authors, after careful investigation, have reached the conclusion that exposure to lowered temperature, of and by itself, may be a complete cause of disease without the intermediation of bacteria. It was therefore planned to subject an animal to sudden and severe lowered temperature and to take note of alterations of function or structure, with special reference to the possibility of increased susceptibility to zymotic disease.

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[6] Buzzard, E. Farquhar, and Greenfield, J. G.: Lethargic Encephalitis; its Sequelæ and Morbid Anatomy, Brain, 1919, xlii, 305.